

## REMARKS

Claims 1-12, 18-27 and 44-49 are pending. Claim 2 has amended for clarity and to enter previous amendment that was not entered. Claims 48 and 49 have been amended to correctly reference claim 19, not claim 1 or 18, and claims 50 and 51 have been newly added in order to overcome the Examiner's objections and to correctly reference the proper claim ( for claims 50 and 51, they properly depend from claim 3). A version showing changes made is attached for the Examiner's convenience. An appendix of pending claims is also attached for the Examiner's convenience.

### Rejections based under 35 U.S.C § 103(a)

Claims 1-6, 8-10, 18-23, 25-27 and 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410 B1, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863,722, filed June 7, 1995).

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the microspheres not having an optical signature as taught by Brenner et al. and the non-optical encoding taught by Walt et al. to the microsphere compositions of Walt et al. and to provide at least one subpopulation of microsphere without an optical signature thereby eliminating the need to provide optical signatures on all the microspheres for the obvious benefits of simplicity. Applicants respectfully traverse.

Walt et al. is directed to a microsphere-based analytic chemistry system. Walt et al. teaches the use of microspheres distributed on the surface of a substrate wherein each microsphere contains an optical signature. Regarding claims 1 and 18, from which all claims depend, Walt et al. is silent with respect to teaching at least one subpopulation of microspheres not having an optical signature.

Brenner et al. is directed to a method of sorting polynucleotides through the use of oligonucleotide tags by specifically hybridizing the tags attached to the polynucleotides to their complements on solid phase supports. Contrary to the Examiner's characterization of Brenner et al. that it discloses microspheres not comprising an optical signature, it does not teach or suggest at least one subpopulation of microspheres within an array, not having an optical signature, an aspect of claims 1 and 18, from which all other claims depend.

In contrast claims 1 and 18 (from which all other claims depend) are directed to an array composition (claim 1) and a method of making an array composition (claim 18) comprising a population of microspheres comprising at least a first and a second subpopulation, wherein at least one of said subpopulations does not have an optical signature.

As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As a preliminary matter, neither Brenner et al. nor Walt et al., alone or in combination, teach or suggest that at least one subpopulation of microspheres within a random array, does not have an optical signature. Although Brenner et al. discloses the use of microspheres on a substrate, nowhere in this reference is there teaching of the use of microspheres within the same random array, wherein at least one subpopulation does not have an optical signature. The

Examiner points to several places in Brenner et al. as support for disclosing microspheres without an optical signature (column 9, lines 62-65; column 19, lines 20-49; column 21, line 15 and column 22, line 61), but nowhere in Brenner et al. is there any teaching or suggestion of a subpopulation of microspheres within an array that does not have an optical signature. Column 9, lines 62-65 of Brenner discusses support characteristics used depending on the conditions in which tags are used, for example “in applications involving successive processing with enzymes, supports and linkers that minimize steric hinderance of the enzymes and facilitate access to substrate are preferred”, Brenner et al., column 9, lines 65-67; column 10, line 1. There is no discussion of the use of different size beads within the same array. Similarly at the other sites of Brenner referenced by the Examiner, there is no teaching or suggestion of the use of a subpopulation of microspheres that does not contain an optical signature. Therefore, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met. Accordingly the rejection is improper and Applicants respectfully request the withdrawal of the rejection.

In addition, in the instant case there is lacking any suggestion or motivation to modify the references or combine reference teachings. As noted briefly above, the Examiner suggests that one of skill in the art would have been motivated to combine references because it was obvious to apply the microspheres not having an optical signature of Brenner et al. and the non-encoding optical signature of Walt with the microsphere compositions of Walt et al. and to provide at least one subpopulation of microspheres without an optical signature for simplicity. See page 4 of the Office Action.

However, Applicants submit that this is a legally incorrect determination of motivation. The mere fact that references can be combined or modified does not render the resultant

combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). There is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention. That is, while Walt et al. describes in the use of microspheres for the detecting the presence or absence of a target, there is nothing cited to in either reference that teaches or suggest the use of at least one subpopulation within a random array that does not contain an optical signature.

The Examiner's attention is respectfully drawn to In re Lee, 61 USPQ2d 1430 (CA FC 2002). In this case, the Examiner rejected the claims under 35 U.S.C. §103 and stated that the required motivation "would be that the automatic demonstration mode is user friendly and it functions as a tutorial". Id at 1435. The Federal Circuit stated that "deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense". The Board's finding must extend to all material facts and must be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to be derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435). In the present case Applicants submit that the Examiner has failed to point to anything specific in the cited references that would suggest or provide the motivation to combine the references or to modify them. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under In re Lee.

In this case, the Examiner has essentially used impermissible hindsight and "common sense" to conclude that the combination of these two references would have been motivated by

“the obvious benefit of simplicity ”. This is legally incorrect under the Federal Circuit’s analysis.

The Examiner makes a very general statement of “obvious benefit”. As noted above in the In re Lee case, “common sense” is not an adequate motivation to combine. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O’Farrell, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Accordingly the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

Claims 7 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863, 722, filed June 7, 1995) as applied to claims 1 and 18 above and further in view of Augenlicht (U.S. Patent No. 4,981,783).

The Examiner states that it would have been obvious to one of ordinary skill in the art to apply the fiducial placement taught by Augenlicht to the method of making an array composition of Walt et al and to place the fiducials to define an edge of the array to thereby align the array for detection as taught by Augenlicht (column 7, lines 33-35) for the expected benefit facilitating detection and identification of the bioactive agent as taught by Augenlicht (column 8, lines 15-26). Applicants respectfully traverse.

The distinctions between Brenner et al., Walt et al. and the claims of the present invention are discussed above and are incorporated at this point by reference.

Augenlicht et al. is directed to detecting the expression of cloned genes by immobilizing nucleic acid from individual clones arranged in a pattern on a substrate such as nitrocellulose and hybridizing nucleic acid probes to the immobilized nucleic acid with subsequent determination

of the level of expression of individual genes in a sample. Augenlicht et al. teaches the use of fiducial markings to locate the position of the individual clones. Augenlicht et al. does not teach the use of fiducials in an array comprising microspheres distributed on a substrate. In addition, Augenlicht et al. does not teach the use of microspheres randomly distributed on the surface of a substrate, wherein at least one subpopulation does not have an optical signature.

Claim 7 depends from claim 1 and claim 24 depends from claim 18, and as stated above both are drawn to either an array composition (claim 1) or a method of making an array composition (claim 18) comprising a population of microspheres comprising at least a first and a second subpopulation, wherein at least one of said subpopulations does not have an optical signature and the use of fiducials, wherein said fiducial is a defined edge of said substrate (claims 7 and 24).

As stated above, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As a preliminary matter, none of the cited art references teach or suggest the use of at least one subpopulation of microspheres, within a random array that does not contain an optical signature. This is an aspect of the claims of the present invention, therefore the requirement that

the prior art reference ( or references when combined) must teach or suggest all the claim limitations has not been met.

In determining the differences between the prior art and the claims, the question under 35 U.S.C 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aerowhip Corp., 713 F. 2d 782, 218 USPQ 698 (Fed. Cir. 1983). Here it is claims 1 or 18 as a whole that must be considered in determining obviousness, not just the differences between the dependent claim limitations and the prior art. For the reasons set forth above, the rejection is improper and the applicants respectfully request the withdrawal of the rejection.

In addition, in the instant case there is lacking any suggestion or motivation to modify the references or combine reference teachings. The Examiner cites to the expected benefit facilitating detection and identification of the bioactive agent as the motivation to combine references to reach the claims of the present invention.

Obviousness is tested by what the combined teachings of the references would have suggested to those of ordinary skill in the art. It cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. And teachings of references can be combined *only* if there is some suggestion or incentive to do so. *In reFine*, 5 USPQ2d 1596, 1599 (CAFC 1988) (quoting *In re Keller*, 208 USPQ 871,881 (CCPA 1981) and *ACS Hosp. Sys. v. Montefiore Hosp.*, 221 USPQ 929, 933 (CAFC 1984)).

Here, there is lacking any suggestion or motivation in the prior art to arrive at methods of making an array composition and an array composition through the use of subpopulations microspheres distributed on the surface of a substrate, wherein at least one subpopulation within

the array does not contain an optical signature, an element of all claims of the present invention. As noted above, there is no motivation and the Examiner has failed to point to anything specific in the cited references that would suggest the motivation to combine Walt with Brenner and Augenlicht to reach the claims of the present invention. In fact, the combination of these references would not produce the methods of Applicant's invention, because they all lack an essential element as stated above.

As noted above in the In re Lee case, "common sense" is not an adequate motivation to combine. It is improper to use an obvious to try approach or to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O'Farrell, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Accordingly the rejection is improper and the Applicants respectfully request the withdrawal of the rejection.

Claim 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863,722, filed June 7, 1995) as applied to claim 1 above and further in view of Chee et al. (U.S. Patent No. 5,795,716, issued August 18, 1998).

The distinctions between Brenner et al., Walt et al. and the claims of the present invention are discussed above and are incorporated at this point by reference.

Chee et al. is directed to a computer system for analyzing fluorescence intensities of hybridized nucleic acid probes as a method of determining unknown bases in nucleic acid sequences. Chee et al. does not teach or suggest the use of microspheres on the surface of a substrate. Furthermore, Chee et al. does not teach the use of fiducials in an array comprising

microspheres on a surface of a substrate or that one of said subpopulations of microspheres does not have an optical signature.

As mentioned above in order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Examiner states that it would have been obvious to modify the composition of Walt et al. with the computer readable memory of Chee et al. and to use the fiducial to position-specifically receive and register a first data image via the computer code for the expected benefit of computer aided improved analysis of bioagents as taught by Chee et al. Applicants respectfully disagree.

As stated above, citing to *In re Lee*, “deficiencies of the cited references cannot be remedied by the Board’s general conclusions about what is “basic knowledge” or “common sense”.

In this case, the Examiner has essentially tried to remedy the deficiencies of the cited references by impermissibly using “common sense” to conclude the combination of these two references leads to computer aided improved analysis of bioagents. This is legally incorrect under the Federal Circuit’s analysis.

There is no suggestion from either Walt et al., Brenner et al. or Chee et al. to teach claims which utilize fiducials in an array comprising microspheres on the surface of a substrate wherein at least one of said subpopulations of microspheres does not have an optical signature. Therefore, the requirement that there be some suggestion or motivation, either in the references themselves

or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings has not been met.

In addition, the cited references do not teach all of the claim limitations. Neither Walt et al., Brenner et al. nor Chee et al., alone or in combination teach or suggest the use of at least one subpopulation of microspheres not having an optical signature, which is an element of both claims 11 and 12 (both claims depend from claim 1). Accordingly, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met for a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request the withdrawal of the rejection.

### CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

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**VERSION SHOWING CHANGES MADE**

2. (amended) An array composition according to claim 1 wherein [each] at least one of said subpopulations comprises a unique optical signature.

48.(amended) A method according to claim [1 or 18] 19, wherein said identifier binding ligand is a protein.

49.(amended) A method according to claim [1 or 18] 19, wherein identifier binding ligand is a nucleic acid.

50.(new) An array composition according to claim3, wherein said identifier binding ligand is a protein.

51.(new) An array composition according to claim 3, wherein identifier binding ligand is a nucleic acid.